with a hydantoinase;

contacting the hydantoin with a D- or L-specific carbamoylase; and

contacting the hydantoin with at least one racemase selected from the group consisting of a hydantoin racemase and carbamoyl racemase,

wherein the contacting is performed under conditions suitable for *in situ* racemisation of the hydantoin or of an N-carbamoyl amino acid.

20. (New) The process according to Claim 19, wherein the contacting of the hydantoin with the hydantoinase, D- or L-specific carbamoylase, and the at least one racemase are performed sequentially or continuously. --

SUPPORT FOR THE AMENDMENT

The above amendment and the additional claims are supported at page 4, line 27, to page 5, line 35, of the specification and the original claims. No new matter is believed to be introduced by the above amendment and the additional claims.

REMARKS

Claims 9 and 11 are cancelled without prejudice. Claims 12-20 are added. Claims 1-8, 10, and 12-20 are pending. Favorable consideration is respectfully requested.

At the outset, Applicants thank Examiner Patterson for rejoining Claims 1-11. Further, Applicants direct the Examiner's attention to the amendment where Applicants have cancelled Claim 11 in favor of Claim 14. Claim 14 now positively recites a method step.

The rejection of Claims 1-11 under 35 U.S.C. § 112, first and second paragraphs, is believed to be obviated by the above amendment and further traversed below. The Office is

reminded that examination of the claims involves determining there precision and clarity, as well as scope of protection, in light of the specification disclosure (see *In re Moore*, 169 USPQ 236 (CCPA 1971)). Applicants respectfully suggest that if such an examination is performed, the 112 rejections would be moot.

Although this rejection is based upon a few distinct points articulated by the Office, the global tenor of this rejection is based on the Office's contention that the skilled artisan would not possess the knowledge at the time of the present invention's filing date to clearly understand, interpret, and perform within the scope of the claimed invention. Interestingly, it should be noted that it is this exact lack of knowledge by the skilled artisan that the Office relies upon to support the obviousness rejection discussed below. Applicants do not understand how the skilled artisan's knowledge is at such a low level to support the 112 rejections, yet the skilled artisan's knowledge is at a level high enough to render the Applicants' claimed invention "obvious"? In light of the above, Applicants are truly confused as to which level of knowledge the skilled artisan possesses according to the Office. Is it low enough to support the 112 rejections or is it high enough to support the 103 rejections?

First, the Office contends that the claims are drawn to a very general hydantoin formula. However, this is not the case at all. In fact, the claims are drawn to a hydantoin in which the only variable region in the entire compound is the acetal moeity. This is clearly indicated in the claims, as well as the specification. Further, Applicants have provided an Example of a compound falling within the claimed hydantoins containing this variable acetal moeity demonstrating its enablement and description. Accordingly, all hydantoins containing this variable acetal moeity are claimed, adequately described, and enabled.

Second, the Office contends that the phrase "conditions suitable for *in situ* racemisation" is not enabled and described. In order to clarify, Applicants direct the Office's attention to page 6, lines 4-13, of the specification which clearly discloses. "During cleavage of hydantoins . . . .hydantoins (of N-carbamoyl amino acids produced) racemise spontaneously" and "hydantoin that remains can be racemised spontaneously". From this disclosure, it is clear that the claimed process must be performed "under conditions suitable for *in situ* racemisation of the hydantoin or of an N-carbamoyl amino acid" as claimed (see Amended Claim 1 above). Further, Applicants have further specified in the claims that the claimed contacting is performed in the presence of "at least at least one racemase selected from the group consisting of a hydantoin racemase and carbamoyl racemase", which is clearly described and enabled. This recitation is described in the specification at page 6, lines 9, and page 5, lines 1-15. Further, the Example (see page 7, lines 13-20) is performed using *Escherichia coli* JM109 described in US 60/157427, which contains "at least at least one racemase selected from the group consisting of a hydantoin racemase and carbamoyl racemase" (see page 5, lines 5-10, of the specification).

Thirdly, the Office contends that the present application lacks written description and enablement for "contacting the hydantoin with the two enzymes". The Office is directed to page 5, lines 1-4, which clearly disclose that the enzymes may be in the form of "free enzymes" and may contact the hydantoin. Even further, Applicants direct the Examiner's attention to the references cited in the obviousness rejections discussed below, which demonstrate that hydantoin derivatives may be contacted with the hydantoinases and carbamoylases. Accordingly, the level of skill in the art would recognize that "free enzymes" involves direct contact of the hydantoin with a hydantoinases and a carbamoylase. It is important to note that the cited references do not disclose the claimed hydantoins containing

the claimed acetal moeities. In fact, they teach away from using hydantoins containing the claimed acetal moeities.

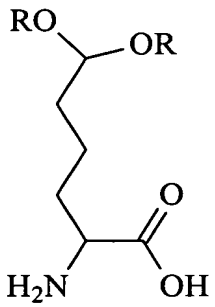
Fourthly, the Office contends that the claims lack descriptive support and/or enablement for the claimed method of making a pharmaceutically or biologically active product. The Office is reminded that Claim 11 is cancelled in favor of Claim 14. Further, the Office is directed to page 1, lines 14-16, page 2, line 30, to page 3, line 2, and page 7, lines 1-5, of the specification, which provides clear description of the claimed method.

Finally, the Office contends that the present application fails to provide description and/or enablement of the enzymes and/or microorganisms in the claims. The Office is reminded that the claimed invention is not drawn to the enzymes and/or microorganisms. Alternatively, the claimed invention is, in part, drawn to methods of using the enzymes and/or microorganisms to produce the compounds of formula 1 (see amended Claim 1 above). The exemplified embodiments of enzymes that may be used according to the invention are fully disclosed at page 5, lines 1-15, where the disclosure states that the exemplified embodiments can be found in US 60/157,427 and US 09/407,062. Further, an Example is provided demonstrating that the claimed method works when utilizing a microorganism described in these references. It appears as if the Office is requesting information under 17 CFR § 1.105. For the Examiner's convenience, Applicants provided herewith, copies of WO/0058449 and WO/12358, which correspond to US 60/157,427 and US 09/407,062. It should be noted that these disclosures, combined with the disclosures of the references cited in the 103 rejection, clearly support that, at the time of the invention, it was well within the skilled artisan to create the claimed enzymes in free form and/or in the form of whole cell catalysts.

In light of the above, Applicants have clearly demonstrated that present application contains proper written description, as well as enablement, for the claimed invention. Accordingly, withdrawal of this ground of rejection is respectfully requested.

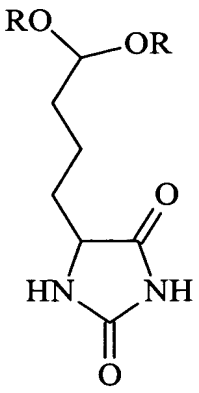
The rejection of Claims 1-11 under 35 U.S.C. § 103(a) over Syldatk et al. and/or Pietzsch et al. is traversed below. Further, Applicants provide herewith a reference (see the Introduction of Wohlfahrt et al. (XP-000991533) attached hereto) in support of Applicants arguments that the claimed invention is not as easy to perform as the Office contends; and therefore, can not possibly be obvious in light of Syldatk et al. and/or Pietzsch et al.

The claimed invention relates to a process of producing a compound containing a specific allysine acetal moeity having the following formula:



(I)

The process is achieved by contacting a hydantoin starting compound containing a specific acetal moeity having the following formula:



(II)

with a hydantoinase, a D or L carbamoylase, and at least one racemase.

In direct contrast, Pietzsch et al. merely discloses how to purify a hydantoinase (see page 182, left column) and how to purify a carbamoylase (see page 183, right column). At best, Pietzsch et al. makes a very broad disclosure that such enzymes may be used to produce optically pure L-amino acids from racemic D,L-5-monosubstituted hydantoin mixtures (see page 185, left column). However, Pietzsch et al. fails to disclose at least one racemase, and fails to disclose that the D,L-5-monosubstituted hydantoin are those that are specifically claimed as formula (II). It should be noted that the Office contends that the some aspects of the claimed invention are not enabled and/or described as discussed above. However, this reference clearly demonstrates the level of skill in the art at the time the present application was filed; and therefore, the claimed invention can be well understood by the skilled artisan in light of the present application's disclosure.

Moreover, the Office relies on Syldatk et al. as a reference. Syldatk et al., at best, discloses that some D,L-5-monosubstituted hydantoins may be used to produce optically pure L-amino acids when contacted with a hydantoinase and a carbamoylase. Like Pietzsch et al.

discussed above, Syldatk et al. also fails to disclose or suggest contacting a D,L-5-monosubstituted hydantoin with at least one racemase, much less the claimed hydantoin starting compound containing a specific acetal moeity.

Most importantly, the Office's attention is directed to Table I in Syldatk et al. at page 324, describing the specific D,L-5-monosubstituted hydantoin tested. More specifically, Table I in Syldatk et al. clearly demonstrates that not all D,L-5-monosubstituted hydantoins are adequate substrates for the production of optically pure L-amino acids. Accordingly, even the Office's own cited art are conflicting, demonstrating that not all D,L-5-monosubstituted hydantoins can easily be utilized. In fact, of the compounds tested by Syldatk et al., the compounds that are listed third and fourth from the bottom of Table I are most similar to the claimed hydantoin starting compound containing a specific acetal moeity (although not homologs thereof) and are shown to be completely inadequate substrates for hydantoinase and carbamoylase activities.

In light of the above references cited by the Office, the Office contends that the claimed invention is obvious. In direct contrast, Applicant respectfully submit that these references further support the patentability of the claimed invention for the following reasons:

1) None of the references cited by the Office disclose or suggest the claimed allysine containing the claimed acetal moeity of formula (I) (see Claim 1 above);

2) None of the references cited by the Office disclose or suggest the claimed hydantoin starting compound containing a specific acetal moeity of formula (II) (see Claim 1 above);

3) None of the references cited by the Office disclose or suggest contacting the claimed hydantoin starting compound containing a specific acetal moeity of formula (II) with the claimed at least one racemase; and

4) At best, Pietzsch et al. suggests that D,L-5-monosubstituted hydantoins may be contacted with hydantoinases or carbamoylases. However, Syldatk et al. discloses that not all D,L-5-monosubstituted hydantoins can serve as adequate substrates of hydantoinases or carbamoylases (see Table I). In fact, the compounds that are not adequate substrates of hydantoinases or carbamoylases are those most closely related to the claimed hydantoin starting compound containing a specific acetal moeity of formula (II).

In light of the above, it is clear that neither Pietzsch et al., nor Syldatk et al., disclose or suggest all of the embodiments of the claims. Further, Syldatk et al. actually discloses that, of the compounds tested therein, the compounds most closely related to the claimed hydantoins may not serve as substrates for hydantoinases or carbamoylases. Therefore, Syldatk et al. actually teaches away from the claimed invention. Accordingly, there exists no *prima facia* case of obviousness and withdrawal of the invention is respectfully submitted.

The rejection of Claims 8 and 9 under under 35 U.S.C. § 112, second paragraph, is believed to be obviated by the above amendment. More specifically, Claim 9 is cancelled in favor of Claim 20 which does not contain the phrase indicated by the office to be indefinite. Further, Claim 8 has been amended to remove this phrase. Both Claims 8 and 20 contain the phrase "the contacting", which has proper antecedent basis in Claim 1 and 19, respectively. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The objection to the disclosure is obviated by the amendment above. More specifically, the phrase indicated by the Office as unclear has been removed. Applicants respectfully direct the Examiner's attention to the sentence directly preceding this "unclear"phrase which demonstrates that the "unclear" phrase is merely redundant to the same due to a clerical error. Accordingly, by removing this phrase, Applicants have merely

removed an unclear phrase which has already been stated in a clear manner by the previous sentence. Accordingly, withdrawal of this ground of objection is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Should anything further be required to place this application in condition for allowance, the Examiner is requested to contact Applicants attorney by telephone.

Respectfully submitted,

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Marked-Up Copy
Serial No: 09/916,501
Amendment Filed on:
HEREWITH

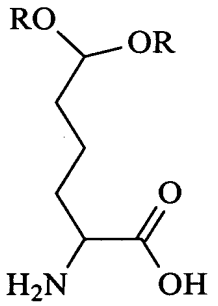
IN THE SPECIFICATION

Please replace the paragraph at page 6, lines 14-18, as follows:

--This reaction may be performed by using separate enzymes [[that which are available separately, which]]. Such enzymes may be in free or immobilised form, be contained within a cell fraction or extract or be enclosed inside of a microorganism (US 60/157427).--

IN THE CLAIMS

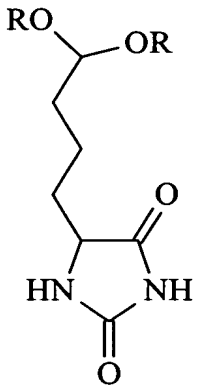
--1. (Amended) A process for the preparation of allysine acetal of the general formula (I)



(I)

comprising:

contacting a hydantoin of the general formula (II):



(II)

wherein in formulae (I) and (II) R represents (C_1-C_8)-alkyl, (C_2-C_4)-alkylene, (C_6-C_{18})-aryl, (C_7-C_{19})- aralkyl, or (C_1-C_8)-acyl,

with a hydantoinase and a D- or L-specific carbamoylase in the presence of at least one racemase selected from the group consisting of a hydantoin racemase and carbamoyl racemase,

under conditions suitable for *in situ* racemisation of the hydantoin or of an N-carbamoyl amino acid.

2. (Amended) The process of Claim 1, wherein at least one of the hydantoinase, a D- or L-specific carbamoylase, or [an enzyme used in racemization] the at least one racemase is [used] in at least one form selected from the group consisting of free form, [in] immobilized form, [as a] cell fraction form, [or] cell extract form, [or] and in a form enclosed in a cell.

3. (Amended) The process of Claim 1, wherein the in situ racemization is spontaneous, enzyme-catalysed, or both.

4. (Amended) The process according to Claim 1,

wherein the hydantoin racemase, the hydantoinase, and the L- or D- specific carbamoylase are present in a total cell catalyst [is used, and wherein said total cell catalyst is from a cell that comprises a cloned gene coding for a hydantoin racemase, a hydantoinase, and an L- or D- specific carbamoylase].

5. (Amended) The process according to Claim 4,

wherein [said] the total cell catalyst comprises an L-specific carbamoylase.

6. (Amended) The process according to Claim 4,

wherein

the total cell catalyst is a recombinant bacterium.

7. (Amended) The process according to Claim 6, wherein [said] the recombinant bacterium is *[E. coli] Escherichia coli*.

8. (Amended) The process according to Claim 1

wherein

the [reactions are] contacting is carried out in an enzyme-membrane reactor.

10. (Amended) The process according to Claim 1, [further comprising] wherein the contacting is performed in the presence of a metal salt.

--Claims 9 and 11 are cancelled.--

--Claims 12-20 are added.--